

Methods for producing large numbers of compounds have grown in popularity since the advent of modern techniques of combinatorial chemistry. The present invention represents an advance over previously-known combinatorial methods for producing compounds.

For example, most previously-known methods for producing large combinatorial libraries of compounds involved the use of compounds coupled to solid supports, such as resin beads. Solid-phase synthesis techniques have been used for complex synthesis for many years. One advantage of such techniques is the ability to use excess reagents in order to ensure that reactions proceed to completion; this is less feasible for solution-phase reactions because it is cumbersome to separate the excess reagents from a desired solution-phase product. A solid support makes handling and purification of compounds relatively simple; the solid support can be separated from any excess liquid reagents or solvents (for example, by filtration) when a reaction is complete, and the beads can be washed with solvents to further purify the desired compounds. Thus, in the early development of combinatorial chemistry, solid-phase techniques were used in an effort to make the handling of hundreds or thousands of different compounds and reaction mixtures more feasible.

However, solid-phase techniques suffer from certain disadvantages. For example, solid-phase chemistries can only be applied when it is possible to attach the compounds to a solid support; this imposes limitations on the types of reactions that can be employed in the synthesis and on the types of molecules that can be synthesized. Also, when a solid-phase synthesis is complete, the compounds must be cleaved from the solid support if it is desired to obtain the compounds in solution; this cleavage requires an extra step. Additionally, in some solid-phase synthesis methods, the compounds are produced in mixtures (on beads), and the identity of the compound on a particular bead must be determined by deconvolution (which can be complicated and may also indicate only the product that should be present, rather than directly determining the product that is present) or by analysis, further complicating the method.

The historical acceptance of solid-phase combinatorial chemistry techniques demonstrates that the advantages of such techniques were considered to be sufficient to outweigh the disadvantages. For example, despite the existence of well-known solution-phase reactions, combinatorial chemists were evidently willing to accept the limitations imposed upon reaction conditions by solid-phase synthesis, e.g., as described above, in order to avoid the perceived disadvantages of solution-phase synthesis with respect to the

production of large combinatorial libraries..

In contrast to solid-phase synthesis methods, the present invention uses solution-phase synthesis to provide compounds in solution. The compounds are produced in solution, so they need not be cleaved from any solid support; moreover, any solution-phase reaction technique can potentially be applied to the methods of the invention. Furthermore, the claimed methods produce compounds in a spatially-addressable array, so the identity of the desired compound in a particular array location is known and need not be deduced through analysis (although analysis can be used to confirm that the compound is, in fact, present).

**Rejection of claims under 35 USC 112, second paragraph**

Claims 10-13, 17, 18, and 20-25 were rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. Applicants respectfully traverse these rejections and submit that the rejections do not apply to the pending claims.

Claims 10, 11 and 22 were rejected as being vague and indefinite by reciting the phrase “spatially-addressable array.” Applicants submit that the phrase “spatially-addressable” is not vague and indefinite. As described in the subject specification, a spatially-addressable array is an array in which individual addresses (i.e., reaction vessels) are separated in space and can be accessed (addressed) individually. See, for example, the specification at pages 27-29 (the Example); Figures 1 and 2; and page 46, Table 4. Moreover, the specification, at page 9, lines 30-31, describes a “spatial address” as “a position in the array defined by unique Cartesian coordinates.” Thus, a “spatially-addressable array” is an array in which the individual addresses are defined by unique Cartesian coordinates. One of ordinary skill in the art would clearly understand the phrase “spatially-addressable array” in light of the teachings of the present specification.

The phrase “structural diversity elements” was also objected to in the Office Action. Applicants do not agree that this term is vague and indefinite. Structural diversity elements refer to the common variable structural elements of a molecular construct, and comprise moieties which are attached to the molecular core or backbone. The structural diversity elements are varied to produce the compounds of the array. See, for example, the specification at page 9, lines 25-27, and pages 21-26. Furthermore, a wide variety of different structural diversity elements can be utilized in the present invention as claimed, such that use of this generic term is appropriate.

Claim 10 was rejected as being vague and indefinite by reciting “a) providing a plurality of reaction vessels organized into the first and [second] sub-array...” This rejection is traversed. Claim 10, as presently pending, recites: “(a) providing at least 500 reaction vessels organized into at least first and second sub-arrays . . .”. As stated in the specification, e.g., at page 9, lines 32-35, a sub-array is a set of spatial addresses within a given array; in other words, a sub-array is a subset of an array. Although vessels (or addresses or compounds) are spatially separated from one another, they can nevertheless be grouped together in an array, and an array can include two or more sub-arrays. As recited in claim 10, reactants are added to each of the reaction vessels such that the compounds composing each sub-array differ from one another by one change in a structural diversity element. The reactants can be added to each of the reaction vessels according to any method known in the art; for example, reactants can be added to the reaction vessels using a pipette or multiple pipettes (see, e.g., specification at page 14, lines 1-4). The method of adding reactants to the reaction vessels is not important, provided that, as recited in claim 10, the compounds composing each sub-array differ from one another by one change in a structural diversity element, and the compounds composing the first sub-array each have at least one common structural diversity element and the compounds composing the second sub-array each have at least one common structural diversity element. To achieve this result, different reagents are added to different reaction vessels, as described throughout the specification (see, e.g., page 15, lines 13-22; the Examples; and Tables 1- 4). Applicants contend that one of ordinary skill in the art would understand this claim language and that the amended claim is not vague or indefinite.

Claims 11 and 22 were rejected as being vague and indefinite by reciting “apportioning into reaction vessels identifiable by their spatial addresses”. Applicants do not agree. As the specification makes clear, a spatial address refers to the position of a vessel or compound in an array. One of ordinary skill in the art would immediately realize that the reactants can be apportioned into these vessels in order to form the compounds. Accordingly, this language cannot be vague or indefinite.

The Examiner also requested clarification of claim 11 in step b). Applicants submit that the claim language is clear as written. Claim 11, at step b), recites the step of “concurrently reacting said first and second reactants in each of the plurality of reaction vessels under solution phase conditions wherein the first and second reactive groups react with one another by an addition reaction to form a compound”. Claim 11, therefore, clearly requires that a reaction occurs whereby first and second reactants are reacted together within

each of the plurality of reaction vessels. Applicants respectfully submit that this language is clear and is not indefinite.

Claim 12 was rejected as being vague and indefinite for reciting “... formatting the contents of the reaction vessels into a spatially-addressable array.” In a previous response, claim 12 was amended to provide that the further formatting step can occur after step a) or step b); that is, that the formatting step can occur after the apportioning step or after the reacting step. Applicants respectfully submit that this language is clear and unambiguous. Furthermore, the present specification, e.g., at page 28, lines 14 - 34, describes one example of formatting of an array according to the amended claims. In that example (which is but one embodiment of the claimed invention), the contents (or a portion thereof) of the reaction vessels were formatted into new vessels prior to analysis. The formatting step can result in the compounds being rearranged, or, alternatively, the relative positions of the compounds may be the same after formatting as it was prior to formatting. Applicants respectfully urge that the pending claims are not vague and ambiguous.

Claims 20 and 21 were rejected as unclear for reciting “wherein the compounds of the array provide structure-activity relationships useful in the selection . . .”. Claims 20 and 21, as amended, are directed to an embodiment of the invention in which the arrays produced according to the methods of the invention are screened to provide structure-activity relationships useful for the elucidation of optimum compounds. The screening of compounds for such purposes is well known, and one of ordinary skill in the art would be able to perform the claimed methods using no more than routine experimentation. Accordingly, Applicants submit that this rejection does not apply to the pending claims.

Accordingly, Applicants urge that the claims are not vague and ambiguous, and that all rejections under 35 USC 112, second paragraph should be withdrawn.

#### **Rejection of claims under 35 USC 103(a)**

Claims 10-13, 17, 18 and 20-25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Pirrung et al. (Advance ACS Abstract, January 1, 1995) (“Pirrung”) and Gallop et al. (J. Med. Chem., vol. 37, number 9, April 29, 1994, pages 1233-1251) (“Gallop”). The rejection is respectfully traversed.

The pending claims are directed to methods for making arrays of at least 500 compounds in solution phase. All the pending claims require that reactants are added to reaction vessels, and the reactants are then reacted in the reaction vessels under solution-phase conditions to form an array of compounds in solution.

In contrast, the Pirrung reference is an abstract that relates to the preparation of 54 carbamate compounds, in “sub-libraries”. Pirrung neither teaches nor discloses methods for the generation of solution phase libraries as presently claimed by applicants. Moreover, Pirrung provides no experimental details about the structures of the compounds, nor about the specific methods by which the compounds were made.

The Examiner has cited Pirrung as teaching the solution-phase synthesis of compounds. As described above, Pirrung reference does not describe the method by which the compounds were prepared. Assuming, *arguendo*, that Pirrung does describe the solution-phase synthesis of compounds, Pirrung does not teach or suggest the synthesis of at least 500 different compounds in solution phase (as the Examiner concedes).

Gallop is a review article describing combinatorial chemistry technology. The Examiner states that Gallop describes the mathematical formula for calculating the number of compounds that can be produced in a combinatorial synthesis; the Examiner states that “the reference teaches that using 100 building blocks permits the *theoretical* synthesis of 100 million tetrameric chemical entities [citation omitted]. Thus, a combinatorial library of 500 different compounds can be prepared using the formula given by Gallop et al.” (emphasis added).

The Examiner continues by stating that Pirrung does not specifically teach split synthesis, but that Gallop does teach split synthesis. The Examiner then concludes that “it would have been obvious to a person skilled in the art at the time the invention was made to use the split method synthesis with indexed library synthesis taught by Pirrung et al and use 500 different vessels to obtain 500 different compounds in the library, because Pirrung et al teach indexed libraries by preparing 15 different libraries, and Gallop et al teach a method for split synthesis and a method to determine the number of individual units in a library.”

Applicants respectfully traverse the above rejection. The combination suggested by the Examiner is not apt; in fact, not only would the proposed combination not be obvious, it would not result in the claimed invention.

Applicants believe that the Examiner has to some extent misunderstood the teachings of Gallop. Gallop does teach “split synthesis”; however, the method that Gallop describes (at page 1242 and Figure 2) is not a *solution-phase* synthesis method at all. Instead, the Gallop reference is describing the synthesis of chemical compounds attached to a plurality of *solid-phase* supports (e.g., resin beads). These individual solid-phase support beads, as described by Gallop, can be combined into a single reaction vessel (e.g., for purification of the solid-phase reactants), and then subsequently the supports in one reaction vessel can be

“split” or apportioned among many reaction vessels for subsequent reaction steps. This method is well known, and is well suited for the generation of many compounds bound to solid supports. It is not, however, applicable to solution-phase synthesis, in which the “splitting” of some compounds (but not others) from among a mixture of compounds, would be difficult if not impossible.

Thus, the Examiner is proposing to combine a method known for use in solid-phase synthesis (from Gallop), with what is (apparently) a solution-phase synthesis as described in Pirrung. This combination would be inoperative. An *inoperative* combination of references cannot render obvious the claimed invention. The Federal Circuit has clearly stated that combination of references is improper unless the references themselves provide both a motivation to combine the references, and a reasonable expectation that such a combination would be successful (see, e.g., *In re Dembiczak* 175 F.3d 994, 50 USPQ2d 1614). Accordingly, Applicants submit that the claimed invention is not, and cannot be, obvious in light of the cited references, as an inoperative combination cannot provide either motivation to combine or an expectation of success (see, e.g., *Robotic Vision Systems, Inc. v. View Engineering, Inc.*, 189 F.3d 1370, 51 USPQ2d 1948 (Fed. Cir. 1999) “[t]he party seeking a holding of invalidity based on a combination of two or more prior art teachings must show some motivation or suggestion to combine the teachings”).

Moreover, even if the combination of references suggested by the Examiner is not inoperative, one of ordinary skill in the art would not be motivated to combine the references as cited by the Examiner. Gallop does not teach or suggest the solution-phase synthesis of compounds in combinatorial reactions, as claimed. As described above, the “split synthesis” of Gallop is a solid-phase technique, not a solution-phase technique; in contrast, Pirrung appears to describe a synthesis of mixtures of compounds in solution. One of ordinary skill in the art would not be motivated to combine the references cited in the way suggested by the Examiner, to arrive at the claimed invention.

In addition, the skilled artisan could not have a reasonable expectation of success in combining the references in the manner suggested by the Examiner. Applicants respectfully point out that while Gallop does describe a mathematical formula for determining the number of compounds produced by a combinatorial synthesis, and provides the example of 100 million tetrameric entities, Gallop does not provide any solution-phase method by which such large numbers of compounds could be prepared. As described above, the solid-phase methods described by Gallop are not applicable to the solution-phase methods of the present claims. Pirrung itself does not teach or suggest that libraries of at least 500 compounds could be prepared by the (vaguely described) methods of that reference. Gallop

does not support the proposition that the method of Pirrung could be combined with another method, or indeed be modified in any way, to arrive at the claimed invention. The Examiner's unsupported statement that "a combinatorial library of 500 different compounds can be prepared using the formula given by Gallop et al." does not demonstrate any expectation that the methods of the Gallop paper could be modified or combined with the methods of Pirrung in any way; the mathematical formula of the Gallop paper is no more than a means for calculating numbers of compounds; it does not *enable* the synthesis of compounds. Accordingly, there could be no reasonable expectation that such a combination would be successful, and the skilled artisan could not have been motivated to combine the references as suggested by the Examiner.

For at least the above reasons, Applicants submit that the rejections based on Pirrung and Gallop have been overcome and should be withdrawn.

**Conclusion**

Applicants respectfully submit that the entire application is now in condition for allowance, early notice of which would be appreciated.

No fee is believed to be due for the claim changes of this response. Should any fees be required, please charge them to Pennie & Edmonds LLP deposit account no. 16-1150.

Respectfully submitted,

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